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Transformation of 1-(Acyl)(2-haloethyl)amino-9,10-anthraquinones into 1-(2-Acyloxyethylamino)-9,10-anthraquinones

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Abstract—Acylation of 1-(2-haloethylamino)-9,10-anthraquinones gave 1-[(2-haloethyl)(aroyl, hetaroyl, or acetyl)amino]-9,10-anthraquinones which were converted into the corresponding 1-[2-(aroyloxy, hetaroyloxy, or acetoxy)ethylamino]-9,10-anthraquinone on keeping in dimethylformamide. According to the experimental data (including those obtained by kinetic study), the transformation involves intramolecular migration of the acyl group through aziridinium or oxazolidinium intermediates.

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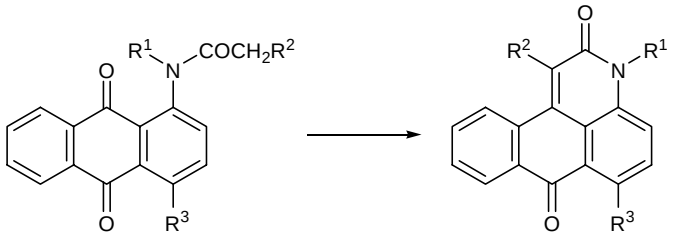
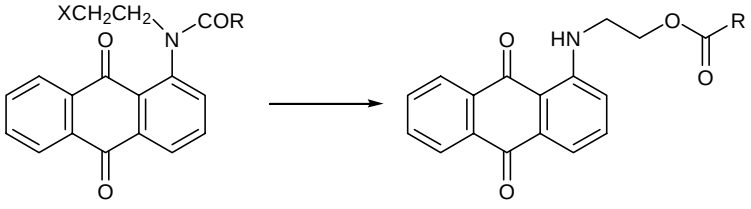
1-Acylamino-9,10-anthraquinones are known to undergo base-catalyzed cyclization to naphtho[1,2,3-*de*]-quinolinones (Scheme 1); here, the R^1 substituent may be both hydrogen atom and alkyl or aryl group, i.e., this substituent is not involved in the cyclization [1]. We have found that 1-[(2-haloethyl)(aroyl, hetaroyl, or acetyl)amino]-9,10-anthraquinones **Ia**–**Ih** obtained by acylation of 1-(2-haloethylamino)-9,10-anthraquinones are converted under analogous conditions into the corresponding 1-[2-(acyloxy)ethylamino]-9,10-anthraquinones **IIa**–**IIg** (Scheme 2). The transformation **I**→**II** occurs under mild conditions (20–50°C) even in the absence of a base (e.g., the transformation **Ig**→**IIg**). Moreover, according to the results of kinetic studies, the rate of the transformation of benzoylamino derivative **Ia** into 1-(2-benzoyloxyethylamino)anthraquinone **IIa** remains almost unchanged over a wide pH range; these data indicate the absence of base catalysis.

Formalistically, the transformation **I**→**II** can be represented as a series of consecutive reactions, including, e.g., hydrolysis of amide **I** to 1-(2-haloethylamino)anthraquinone **III** and subsequent replacement

Scheme 1.



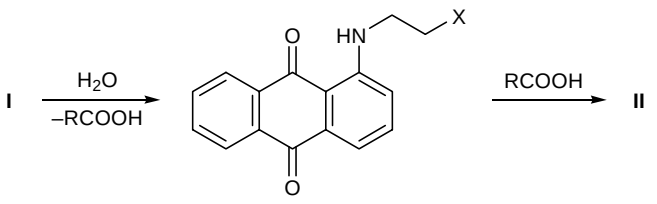
Scheme 2.



Ia–Ih **IIa–IIg**

X = Cl, R = Ph (**a**), 4-ClC_6H_4 (**b**), 3-$O_2NC_6H_4$ (**c**), 4-$O_2NC_6H_4$ (**d**), 2-thienylcarbonyl (**e**), 2-furylcarbonyl (**f**), Me (**g**); X = Br, R = Me (**h**).

Scheme 3.



IIIa, **IIIb**

X = Cl (**a**), Br (**b**).

of the halogen atom by the liberated carboxylate ion (Scheme 3).

However, by special experiments we showed that 1-(2-chloroethylamino)-9,10-anthraquinone reacts with aromatic carboxylic acids at a much lower rate and only in the presence of bases. Another factor ensuring easy transformation of **I** into **II** may be anchimeric assistance [2] by the halogen atom and acylamino group in the α,β-positions, which facilitates formation of aziridinium intermediate **IV** and its subsequent transformation (Scheme 4). We did not detect *N*-acyl-*N*-(2-hydroxyethyl)amino derivatives **V** which should be formed in this case. This result neither supports nor rules out the possibility for formation of aziridinium intermediate **IV**, for the subsequent transformation **V**→**II** may be fast. In addition, we found that the reaction **I**→**II** is intramolecular since amide **Ia** in aqueous DMF is converted exclusively into ester **IIa** even in the presence of a large excess of thiophene-2-carboxylic acid. The kinetic study of the transformation **I**→**II** showed that the rate-determining stage is unimolecular and that electron-acceptor substituents reduce the reaction rate: the rate constants for aroyl derivatives **Ia**–**Id** conform to the Hammett equation (see figure).

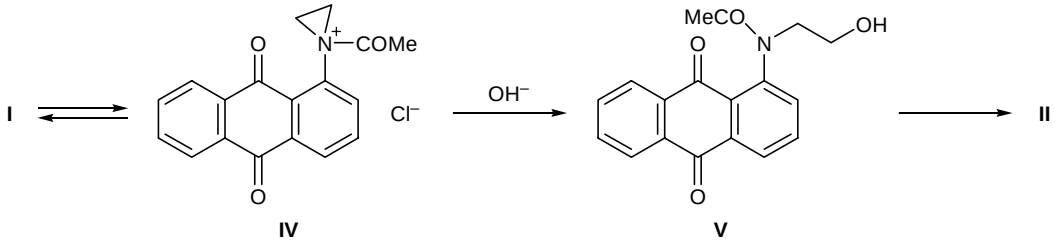
These results, as well as published data [2] on anchimeric assistance with formation of five-membered cyclic intermediates, suggest a probable reaction path shown in Scheme 5. Presumably, the cyclization of amides **I** to intermediates **VI** is the rate-determining stage. In this case, the reaction rate should depend on the halogen nature. In fact, the kinetic data for *N*-acetylamino derivatives **I** showed that the rate of the transformation of 1-[acetyl(2-bromoethyl)amino]-9,10-anthraquinone (**Ih**) into ester **IIg** was higher by a factor of 22.3 than the rate of the transformation of 2-chloroethyl-substituted analog **Ig**. However, the obtained data do not allow us to unambiguously choose between the two possible paths, **I**→**IV**→**V**→**II** and **I**→**VI**→**VII**→**II**.

Thus we have revealed a new transformation of 1-acylamino-9,10-anthraquinones. We have to elucidate whether the observed reaction is typical of other *N*-(2-haloethyl) carboxamides and obtain unambiguous experimental proofs for one or another mechanism of such reactions.

EXPERIMENTAL

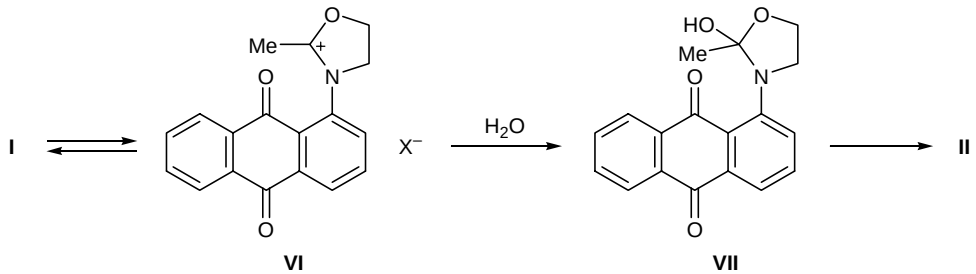
The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer relative to tetramethylsilane as internal reference. The progress of reactions and the

Scheme 4.



IV **V**

Scheme 5.



VI **VII**

X = Cl (**a**), Br (**b**).

purity of products were monitored by TLC on Silufol plates using tolune–acetone (10:1) as eluent. The kinetics of the transformation of amides **Ia**–**Id**, **Ig**, and **Ih** into esters **IIa**–**IId** and **IIg** were studied by spectrophotometry using a Specord UV-Vis instrument at 50°C for **Ia**–**Id** and 25°C for **Ig** and **Ih**. The concentration of esters **IIa**–**IId** and **IIg** was determined at their long-wave absorption maxima (λ 510 nm). Kinetic experiments were performed in 2-cm cells; the concentration of initial amides **Ia**–**Id**, **Ig**, and **Ih** was 0.5×10^{-4} M; 50% aqueous DMF, pH 4.8. The rate constants were calculated by standard procedure [3]; average values from three parallel runs for each transformation were determined. The apparent rate constants k_{ap} are given below:

Compound no.	**Ia**	**Ib**	**Ic**	**Id**	**Ig**	**Ih**
$k_{ap}\times10^4$, s^{-1}	6.22	4.23	1.21	1.38	1.30	29.0

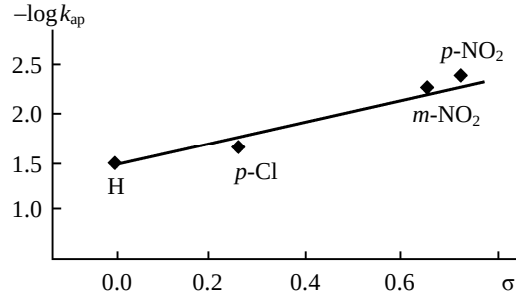
The transformation **Ia**→**IIa** at different pH values (4.0 to 11.6) was studied in a similar way using aqueous DMF buffers prepared from a 0.2 M solution of Na_2HPO_4 and a 0.1 M solution of citric acid [4]. The following values of $\log k_{ap}$ were obtained (k_{ap}, s^{-1}).

pH	4.0	4.8	7.6	10	11.6
$-\log k_{ap}$	3.16	3.20	3.12	3.07	3.25

We failed to isolate compounds **Ig** and **Ih** as individual substances; therefore, their transformation into ester **IIg** was studied as follows: compound **IIIa** (5.286 mg) or **IIIb** (6.129 mg) was dissolved on heating in 10 ml of acetic anhydride, the mixture was kept until the optical density at λ 400 nm no longer increased, a 0.270-ml portion of the mixture was transferred into 10 ml of 50% aqueous DMF to obtain a solution with a concentration of 0.5×10^{-4} M, and the optical density at λ 510 nm (compound **IIg**) was measured.

1-(2-Bromoethylamino)-9,10-anthraquinone (**IIIb**) was synthesized as described in [5].

1-(2-Chloroethylamino)-9,10-anthraquinone (IIIa). 1-(2-Hydroxyethylamino)-9,10-anthraquinone, 5 g (18 mmol) was dissolved in 15 ml of pyridine, the solution was cooled, and 5 ml of benzenesulfonyl chloride was added. The mixture was stirred for 20 min at 70°C and cooled, and the red precipitate was filtered off and washed with ethanol. Yield 5.07 g (95%), mp 179–180°C [5]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.65–3.80 m (4H, CH_2CH_2), 7.05–8.30 m (7H, H_{arom}), 9.98 br.s (1H, NH).



Correlation between the $-\log k_{ap}$ values and Hammett constants σ (ρ = –0.9260, r = 0.9891, s = 0.0225).

1-[Acyl(2-haloethyl)amino]-9,10-anthraquinones Ia–If (*general procedure***).** A mixture of 10 mmol of 1-(2-chloroethylamino)-9,10-anthraquinone and 17 mmol of the corresponding acyl chloride in 2 ml of nitrobenzene was stirred for 30–40 h at 150°C. The mixture was cooled, and the yellow precipitate was filtered off, washed with anhydrous diethyl ether, and recrystallized from toluene.

***N*-(2-Chloroethyl)-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)benzamide (Ia).** Yield 2.57 g (63%), mp 205–206°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.76–3.89 m (2H, CH_2Cl), 4.57–4.64 m and 4.09–4.15 m (2H, CH_2N), 6.97–8.28 (12H, H_{arom}). Found, %: C 71.10; H 4.21; N 3.56. $C_{23}H_{16}ClNO_3$. Calculated, %: C 70.86; H 4.10; N 3.59.

4-Chloro-*N*-(2-chloroethyl)-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)benzamide (Ib). Yield 2.67 g (60%), mp 202–203°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.80–3.82 m (2H, CH_2Cl), 3.91–3.97 m and 4.40–4.49 m (2H, CH_2N), 7.30–8.22 (11H, H_{arom}). Found, %: C 65.11; H 3.52; N 3.21. $C_{23}H_{15}Cl_2NO_3$. Calculated, %: C 65.09; H 3.53; N 3.30.

***N*-(2-Chloroethyl)-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-3-nitrobenzamide (Ic).** Yield 2.73 g (60%), mp 220–221°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.71–3.80 m (2H, CH_2Cl), 4.90–3.99 m and 4.45–4.50 m (2H, CH_2N), 7.36–8.20 (11H, H_{arom}). Found, %: C 63.45; H 3.46; N 6.14. $C_{23}H_{15}ClN_2O_5$. Calculated, %: C 63.52; H 3.45; N 6.44.

***N*-(2-Chloroethyl)-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-4-nitrobenzamide (Id).** Yield 2.82 g (62%), mp 218–220°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.77–3.86 m (2H, CH_2Cl), 3.90–3.95 m and 4.45–4.51 m (2H, CH_2N), 7.43–8.22 (11H, H_{arom}). Found, %: C 63.75; H 3.46; N 6.19. $C_{23}H_{15}ClN_2O_5$. Calculated, %: C 63.52; H 3.45; N 6.44.

***N*-(2-Chloroethyl)-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)thiophene-2-carboxamide (Ie).** Yield

2.69 g (65%), mp 198–200°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.72–3.82 m (2H, CH_2Cl), 3.90–3.95 m (2H, CH_2NH), 6.65–6.80 d (3H, thiophene, J = 5.0 Hz), 7.50–8.37 (7H, H_{arom}). Found, %: C 63.39; H 3.46; N 3.68. $C_{21}H_{14}ClNO_3S$. Calculated, %: C 63.71; H 3.53; N 3.53.

***N*-(2-Chloroethyl)-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)furan-2-carboxamide (If).** Yield 2.06 g (52%), mp 212–214°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.72–3.82 m (2H, CH_2Cl), 3.90–3.95 m (2H, CH_2NH), 6.60–6.70 d (3H, furan, J = 5.0 Hz), 7.50–8.37 (7H, H_{arom}). Found, %: C 66.47; H 3.73; N 3.97. $C_{21}H_{14}ClNO_4$. Calculated, %: C 66.40; H 3.68; N 3.68.

1-(2-Acyloxyethylamino)-9,10-anthraquinones IIa–IIf (*general procedure*). Amide **Ia**–**If**, 1 g, was added under stirring to a mixture of 20 ml of DMF and 0.4 g (2.8 mmol) of potassium carbonate, and the mixture was stirred for 3–4 h at 50°C. The mixture was diluted with 20–40 ml of water, and the red solid was separated and recrystallized from toluene.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl benzoate (IIa). Yield 0.88 g (93%), mp 167–168°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.85 q (2H, CH_2NH, J = 5.0 Hz), 4.60 t (2H, CH_2O, J = 5.0 Hz), 7.45–8.20 (12H, H_{arom}), 9.91 br.t (1H, NH, J = 5.0 Hz). Found, %: C 75.38; H 4.65; N 3.56. $C_{23}H_{17}NO_4$. Calculated, %: C 74.39; H 4.58; N 3.77.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl 4-chlorobenzoate (IIb). Yield 0.74 g (82%), mp 189–192°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.85 q (2H, CH_2NH), 4.60 t (2H, CH_2O), 7.40–8.30 (11H, H_{arom}), 9.91 s (1H, NH). Found, %: C 67.91; H 3.91; N 3.35. $C_{23}H_{16}ClNO_3$. Calculated, %: C 68.06; H 3.94; N 3.45.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl 3-nitrobenzoate (IIc). Yield 0.81 g (85%), mp 175–176°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.88 q (2H, CH_2NH, J = 5.5 Hz), 4.62 t (2H, CH_2O, J = 5.5 Hz), 7.50–8.40 (11H, H_{arom}), 9.91 br.t (1H, NH, J = 5.5 Hz). Found, %: C 66.90; H 3.90; N 6.56. $C_{23}H_{16}N_2O_6$. Calculated, %: C 66.34; H 3.84; N 6.61.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl 4-nitrobenzoate (IId). Yield 0.78 g (83%), mp 200–201°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.88 q (2H, CH_2NH, J = 5.5 Hz), 4.62 t (2H, CH_2O, J = 5.5 Hz), 7.50–8.40 (11H, H_{arom}), 9.90 br.t (1H, NH, J = 5.5 Hz). Found, %: C 66.30; H 3.86; N 6.52. $C_{23}H_{16}N_2O_6$. Calculated, %: C 66.34; H 3.84; N 6.61.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl thiophene-2-carboxylate (IIe). Yield 0.68 g (72%), mp 150–152°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.83 q (2H, CH_2NH, J = 5.0 Hz), 4.53 t (2H, CH_2O, J = 5.0 Hz), 7.30–8.20 (10H, H_{arom}), 9.91 br.t (1H, NH, J = 5.0 Hz). Found, %: C 66.65; H 3.94; N 3.80. $C_{21}H_{15}NO_4S$. Calculated, %: C 69.80; H 4.15; N 3.87.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl furan-2-carboxylate (IIe). Yield 0.76 g (80%), mp 157–158°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.80 q (2H, CH_2NH), 4.50 t (2H, CH_2O), 6.70–8.20 (10H, H_{arom}), 9.85 br.s (1H, NH). Found, %: C 68.91; H 4.09; N 3.95. $C_{21}H_{15}NO_5$. Calculated, %: C 70.04; H 4.34; N 4.05.

2-(9,10-Dioxo-9,10-dihydroanthracen-1-ylamino)-ethyl acetate (IIg). *a*. A solution of 2.85 g (10 mmol) of compound **IIIa** in 6 ml of acetic anhydride was heated to the boiling point over a period of 5 min. The mixture was cooled and poured onto ice, and the red precipitate was filtered off, washed with ethanol, and purified by recrystallization from toluene.

b. Following an analogous procedure, compound **IIg** was obtained from bromo derivative **IIIb**. Yield 2.62 g (85%), mp 160–161°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.10 s (3H, CH_3); 3.63 q (2H, CH_2N, J = 6.0 Hz); 4.35 t (2H, CH_2O, J = 6.0 Hz); 7.35–7.60 m, 7.54–7.77 m, and 8.19–8.3 m (7H, H_{arom}); 9.87 br.s (1H, NH). Found, %: C 69.70; H 4.78; N 4.57. $C_{18}H_{15}NO_4$. Calculated, %: C 69.90; H 4.85; N 4.53.

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REFERENCES

1. Gorelik M.V., *Khimiya antrakhinonov i ikh proizvodnykh*. (Chemistry of Anthraquinones and Their Derivatives), Moscow: Khimiya, 1983, p. 155.
2. March, J., *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, New York: Wiley, 1985. Translated under the title *Organicheskaya khimiya*, Moscow: Mir, 1987, vol. 2, p. 29.
3. Zhdanov, Yu.A. and Minkin, V.I., *Korrelyatsionnyi analiz v organicheskoi khimii* (Correlation Analysis in Organic Chemistry), Rostov-on-Don: Rostov. Gos. Univ., 1966, p. 470.
4. Perel'man, V.I., *Kratkii spravochnik khimika* (Brief Chemist's Handbook), Moscow: Khimiya, 1964, p. 330.
5. Fokin, E.P., Russkikh, S.A., and Russkikh, V.V., *Izv. Sib. Otd. Akad. Nauk, Ser. Khim*., 1965, no. 11, p. 121.